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L4: Entry 6 of 9 File: USPT Nov 16, 1993

US-PAT-NO: 5262325
DOCUMENT-IDENTIFIER: US 5262325 A

TITLE: Method for the enzymatic neutralization of heparin

DATE-ISSUED: November 16, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zimmermann; Joseph J.	Elm Grove	WI		
Lewis; N. Tracey	Brossard			CAX
Heft; Robert A.	Ville St. Laurent			CAX

US-CL-CURRENT: 435/269; 435/13, 435/200

CLAIMS:

We claim:

1. A method to eliminate the physiological effects of heparin on blood components in a mixture of blood components and heparin comprising

contacting blood components containing heparin with a bacterial heparinase preparation,

wherein the heparinase preparation is free of an anticoagulant component prior to mixing of the heparinase preparation with the heparin,

wherein the anticoagulant component does not bind to a polysulfated resin at pH 7.0, conductivity between 3 and 12 mmhos, and the heparinase does bind to a polysulfated resin at pH 7.0, conductivity between 3 and 12 mmhos, and

wherein the heparinase preparation free of an anticoagulant component has an optimal activity at pH=6.5 to 7.0; salt concentration=0.1M, and 37.degree. C.

2. The method of claim 1, wherein the heparinase is purified from cultures of Flavobacterium heparinum chromatography using a polysulfated resin.

3. The method of claim 2 wherein the heparinase is eluted from the affinity resin by increasing the conductivity of the eluent such that the eluted heparinase fraction is free of a Flavobacterium heparinum component inhibiting coagulation.

4. The method of claim 1 wherein the blood contains low molecular weight heparinum.

5. The method of claim 1 wherein the heparinase formulation is prepared by lyophilizing 0.05 to 3.0 IU anticoagulant free heparinase in the presence of 0.5-1.0 mg ammonium sulfate/IU heparinase which has been placed within containers suitable for the collection or incubation of blood or plasma samples.

6. The method of claim 5 wherein the containers are selected from the group consisting of blood collection tubes, pipet tips, fluid transfer devices and syringes.

7. The method of claim 1 wherein the blood sample is incubated with the lyophilized heparinase formulation for between 1 and 3600 seconds at a temperature between 2.degree. and 41.degree. C. prior to the initiation of a hematological test.

8. The method of claim 7 wherein the test relies on the formation of a blood clot as its endpoint.

9. The method of claim 1 wherein the heparinase formulation is prepared by lyophilizing 0.05 to 300 IU anticoagulant free heparinase in the presence of 0.5-1.0 mg ammonium sulfate/IU heparinase which has been placed within a container further comprising resolubilizing the heparinase with a physiologically compatible solution.

10. The method of claim 1 further comprising injecting intravenously the dissolved heparinase formulation into a patient receiving heparin therapy for the purpose of neutralizing the anticoagulant properties of heparin in the bloodstream.

11. The method of claim 10 wherein the heparin is low molecular weight heparin.

Stedman's Medical Dictionary 27th Edition

vein (v?n) [TA]

A blood vessel carrying blood toward the heart; postnatally, all *v.* except the pulmonary carry dark unoxygenated blood. SYN: vena [TA] . [L. *vena*] **accessory cephalic *v.* [TA]** a variable *v.* that passes along the radial border of the forearm to join the cephalic *v.* near the elbow. SYN: *vena* cephalica accessoria [TA] . **accessory hemiazygos *v.* [TA]** formed by the union of the fourth to seventh left posterior intercostal *v.*, passes along the side of the bodies of the fifth, sixth, and seventh thoracic vertebrae, then crosses the midline behind the aorta, esophagus, and thoracic duct, and empties into the azygos *v.*, sometimes in common with the hemiazygos *v.*. SYN: *vena* hemiazygos accessoria [TA] , *vena* azygos minor superior. **accessory saphenous *v.* [TA]** an occasional *v.* running in the thigh parallel to the great saphenous *v.* which it joins just before the latter empties into the femoral *v.*. SYN: *vena* saphena accessoria [TA] . **accessory vertebral *v.* [TA]** a *v.* that accompanies the vertebral *v.* but passes through the foramen of the transverse process of the seventh cervical vertebra and opens independently into the brachiocephalic *v.*. SYN: *vena* vertebralis accessoria [TA] . **accompanying *v.*** SYN: *vena* comitans. **accompanying *v.* of hypoglossal nerve** SYN: *vena* comitans of hypoglossal nerve. **anastomotic *v.*** inferior anastomotic *v.*, superior anastomotic *v.*. **angular *v.* [TA]** a short *v.* at the medial angle of the eye, formed by the supraorbital and supratrochlear *v.* and continuing as the facial *v.*. SYN: *vena* angularis [TA] . **anonymous *v.*** obsolete term for (left and right) brachiocephalic *v.*. **anterior auricular *v.* [TA]** one of several *v.* draining the auricle and acoustic meatus and emptying into the retromandibular *v.*. SYN: *vena* auricularis anterior, *vena* preauricularis. **anterior basal *v.* [TA]** SYN: *vena* basalis anterior [TA] , anterior basal *branch* of superior basal vein (of right and left inferior pulmonary veins)&star, *ramus* basalis anterior venae basalis superioris&star. **anterior cardiac *v.* [TA]** two or three small *v.* in the anterior wall of the right ventricle opening directly into the right atrium independently of the coronary sinus. SYN: venae cardiacae anteriores [TA] . **anterior cerebral *v.* [TA]** small *v.* that parallel the anterior cerebral artery and drain into the basal *v.*. SYN: venae anteriores cerebri [TA] . **anterior ciliary *v.* [TA]** several small *v.*, anterior and posterior, coming from the ciliary body. SYN: venae ciliares anteriores [TA] . **anterior circumflex humeral *v.* [TA]** vein accompanying the artery of the same name, passing anterior to the surgical neck of the humerus to enter the axillary vein. SYN: *vena* circumflexa humeri anterior [TA] . **anterior facial *v.*** SYN: facial *v.*. **anterior intercostal *v.* [TA]** tributaries to the musculophrenic or internal thoracic *v.* from the

Stedman's Medical Dictionary 27th Edition

intravenous (I.V., i.v.)

Within a vein or veins. SYN: endovenous.

Stedman's Medical Dictionary 27th Edition

intravascular

Within the blood vessels or lymphatics.

WEST Search History

DATE: Wednesday, May 29, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR			
L7	L6 near (intravascul$9)	0	L7
L6	L5 not l4	3	L6
L5	heparinase$ near administ$8	7	L5
L4	L3 and administ$6	9	L4
L3	L2 and heparinase$	24	L3
L2	(bennett)[IN] OR (cauchon)[IN] or (fink)[in] or (grouix)[in] or (hsia)[in] or (danagher)[in] or (zimmermann)[in]	18403	L2
L1	(bennett)[IN] OR (cauchon)[IN]	8486	L1

END OF SEARCH HISTORY

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Jan 25  BLAST(R) searching in REGISTRY available in STN on the Web
 NEWS  3  Jan 29  FSTA has been reloaded and moves to weekly updates
 NEWS  4  Feb 01  DKILIT now produced by FIZ Karlsruhe and has a new update
                  frequency
 NEWS  5  Feb 19  Access via Tymnet and SprintNet Eliminated Effective 3/31/02
 NEWS  6  Mar 08  Gene Names now available in BIOSIS
 NEWS  7  Mar 22  TOXLIT no longer available
 NEWS  8  Mar 22  TRCTHERMO no longer available
 NEWS  9  Mar 28  US Provisional Priorities searched with P in CA/CAplus
                  and USPATFULL
 NEWS 10  Mar 28  LIPINSKI/CALC added for property searching in REGISTRY
 NEWS 11  Apr 02  PAPERCHEM no longer available on STN.  Use PAPERCHEM2 instead.
 NEWS 12  Apr 08  "Ask CAS" for self-help around the clock
 NEWS 13  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS 14  Apr 09  ZDB will be removed from STN
 NEWS 15  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS 16  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS 17  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS 18  Apr 22  Federal Research in Progress (FEDRIP) now available

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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FILE 'HOME' ENTERED AT 09:28:02 ON 29 MAY 2002

=> file medline caplus embase biosis
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 09:28:14 ON 29 MAY 2002

FILE 'CAPLUS' ENTERED AT 09:28:14 ON 29 MAY 2002
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FILE 'BIOSIS' ENTERED AT 09:28:14 ON 29 MAY 2002
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=> s bennet D?/au or Cauchon E?/au or Fink D?/au or Grouix B?/au or Hsia A?/au or danagher P?/au or Zimmermann J?/au
L1        3125 BENNET D?/AU OR CAUCHON E?/AU OR FINK D?/AU OR GROUIX B?/AU OR
               HSIA A?/AU OR DANAGHER P?/AU OR ZIMMERMANN J?/AU

=> s l1 and heparin or heparinse
L2          43 L1 AND HEPARIN OR HEPARINSE

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3          21 DUP REM L2 (22 DUPLICATES REMOVED)

=> s l3 (P) administ?
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L12 (P) ADMINIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L14 (P) ADMINIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L16 (P) ADMINIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L18 (P) ADMINIST?'
L4           7 L3 (P) ADMINIST?

=> s l4 (P) (iv or intravascular?)
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L13 (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L15 (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L17 (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L19 (P) '
L5           0 L4 (P) (IV OR INTRAVASCULAR?)
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=> dis l4 1-7 ibib abs

L4 ANSWER 1 OF 7 MEDLINE
ACCESSION NUMBER: 96322828 MEDLINE
DOCUMENT NUMBER: 96322828 PubMed ID: 8712450
TITLE: Heparinase I (neutralase) reversal of systemic anticoagulation.
AUTHOR: Michelsen L G; Kikura M; Levy J H; Lee M K; Lee K C; **Zimmermann** J J; Szlam F
CORPORATE SOURCE: Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia, USA.
SOURCE: ANESTHESIOLOGY, (1996 Aug) 85 (2) 339-46.
Journal code: 4SG; 1300217. ISSN: 0003-3022.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 19980206
Entered Medline: 19960912

AB BACKGROUND: Protamine causes multiple adverse reactions. Heparinase I, a specific enzyme that inactivates **heparin**, is a possible alternative to protamine. In this study, the authors examined the efficacy of heparinase I to reverse **heparin**-induced anticoagulation in vitro and compared heparinase I to protamine as an antagonist of **heparin**-induced anticoagulation in dogs. METHODS: In the in vitro study, blood was obtained from the extracorporeal circuits of 12 patients, and activated clotting times were determined after adding different concentrations of heparinase I. In the in vivo study, 24 anesthetized dogs received 300 units/kg **heparin** injected intravenously for 5 s, then 10 min later, 3.9 mg/kg protamine, 5-41 micrograms/kg heparinase I, or the vehicle (n = 4/group) were **administered** intravenously, and activated clotting times and hemodynamics were measured. RESULTS: In the in vitro study, **heparin** concentrations of 3.3 +/- 1.0 (mean +/- SD) units/ml (approximately 0.033 mg/ml; n = 12) were reversed in the blood of patients by heparinase I at concentrations > 0.490 microgram/ml. In the canine study, heparinase at all doses studied and protamine effectively reversed the anticoagulating effects of **heparin** within 10 min of **administration**. Protamine produced adverse hemodynamic effects, whereas heparinase or its vehicle produced no significant change in arterial pressure. CONCLUSION: Both heparinase I and protamine effectively reversed **heparin** anticoagulation. However, as opposed to protamine, heparinase I did not produce any significant hemodynamic changes when given as a bolus to dogs.

L4 ANSWER 2 OF 7 MEDLINE
ACCESSION NUMBER: 95030369 MEDLINE
DOCUMENT NUMBER: 95030369 PubMed ID: 7943773
TITLE: In vitro reversal of **heparin** effect with heparinase: evaluation with whole blood prothrombin time and activated partial thromboplastin time in cardiac surgical patients.
AUTHOR: Despotis G J; Summerfield A L; Joist J H; Goodnough L T; Santoro S A; **Zimmermann J J**; Lappas D G
CORPORATE SOURCE: Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO 63110.
SOURCE: ANESTHESIA AND ANALGESIA, (1994 Oct) 79 (4) 670-4.
Journal code: 4R8; 1310650. ISSN: 0003-2999.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19980206
Entered Medline: 19941110

AB This study was designed to evaluate the potential in vitro use of heparinase to eliminate functionally active **heparin** prior to performing whole blood (WB) prothrombin time (PT) and activated partial thromboplastin time (APTT) assays. A total of 250 U/kg of **heparin** for cardiopulmonary bypass (CPB) was **administered** to 30 cardiac surgical patients in three consecutive, divided doses (20, 80, and 150 U/kg) at 15-min intervals. Blood specimens were obtained prior to **heparin administration** (baseline) and 10 min after each **heparin** dose. After collection, blood specimens were fractionated into three aliquots of which the first was used for determination of **heparin** concentration. After gentle mixing, WB PT and APTT measurements were performed for heparinase (Aliquot 2)- and nonheparinase (Aliquot 3)-treated blood. With consecutive **heparin** doses of 20 and 80 U/kg, WB PT increased from a baseline of 12.3 +/- 0.1 s to 13.3 +/- 0.2 and 18.5 +/- 1.3 s, while WB APTT increased from a baseline of 28.3 +/- 1.1 s to 89.5 +/- 5.4 after the initial **heparin** dose (20 U/kg). When compared to baseline (no **heparin**) results, small, progressive increases in heparinase-treated WB PT (0.7 +/- 0.1, 1.5 +/- 0.1, 2.1 +/- 0.1 s) and APTT (2.3 +/- 0.3, 5.7 +/- 0.4, 9.5 +/- 0.5 s) were seen with increasing **heparin** concentration (0.23, 1.58, and 3.95 U/mL, respectively). Heparinase was highly effective in eliminating the anticoagulant effects of even large amounts of **heparin** in plasma from cardiac surgical patients.(ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:303407 CAPLUS
DOCUMENT NUMBER: 126:272357
TITLE: Use of heparinases to decrease inflammatory responses
INVENTOR(S): Bennett, D. Clark; **Cauchon, Elizabeth**; **Fink, Dominique**; **Grouix, Brigette**; **Hsia, Ariane**; **Danagher, Pamela**; Zimmerman, Joseph
PATENT ASSIGNEE(S): Ibex Technologies Inc., Can.; Bennett, D. Clark; Cauchon, Elizabeth; Fink, Dominique; Grouix, Brigette; Hsia, Ariane; Danagher, Pamela; Zimmerman, Joseph
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9711684 A1 19970403 WO 1996-US15593 19960927
W: AU, BR, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, SG, US, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
CA 2233343 AA 19970403 CA 1996-2233343 19960927
AU 9673791 A1 19970417 AU 1996-73791 19960927
AU 703394 B2 19990325
EP 852491 A1 19980715 EP 1996-936052 19960927
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
JP 11512721 T2 19991102 JP 1996-513723 19960927
US 2001006635 A1 20010705 US 1996-722659 19960927
PRIORITY APPLN. INFO.: US 1995-4622P P 19950929
WO 1996-US15593 W 19960927

AB Heparinase enzymes can be used as a medical treatment to reduce localized inflammatory responses. Treatment of activated endothelium with heparinase inhibits leukocyte rolling, adhesion and extravasation. Most of the **heparin** and heparan sulfate on endothelial cell surfaces and in basement membranes is degraded by exposure to heparinase. In addn., immobilized chemokines, which are attached to **heparin** /heparan sulfate on activated endothelium are solubilized by heparinase digestion. Heparinase can be infused into the vascular system to inhibit accumulation of leukocytes in inflamed tissue and decrease damage resulting from localized inflammations. Targeting of heparinase to activated endothelium can be accomplished through localized **administration** and/or use of genetically engineered heparinase contg. endothelium ligand-binding domains.

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:237498 CAPLUS
DOCUMENT NUMBER: 124:250963
TITLE: Glycosaminoglycan-degrading enzymes for modulation of wound healing processes
INVENTOR(S): **Zimmermann, Joseph**; Vlodavsky, Israel; Bennett, D. Clark; **Danagher, Pamela**; Broughton, Richard
PATENT ASSIGNEE(S): Ibex Technologies R and D, Inc., USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE
WO 9601648 A1 19960125 WO 1995-US8608 19950707
W: AU, CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
US 5997863 A 19991207 US 1994-273109 19940708
CA 2194370 AA 19960125 CA 1995-2194370 19950707
AU 9530949 A1 19960209 AU 1995-30949 19950707
AU 707007 B2 19990701
EP 769961 A1 19970502 EP 1995-926645 19950707
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 10506609 T2 19980630 JP 1995-504443 19950707
PRIORITY APPLN. INFO.: US 1994-273109 19940708
WO 1995-US8608 19950707

AB Glycosaminoglycan-degrading enzymes, including heparinases 1, 2, and 3, as well as chondroitinases AC and B from the Gram neg. bacterial Flavobacterium heparinum, can be used either sep. or in combination to manipulate cell proliferation. In one embodiment, heparinases are **administered** to degrade heparan sulfate components of the extracellular matrix, thereby allowing the **heparin**-binding growth factors which are stored in the extracellular matrix to migrate to adjacent cells. The mobility of chemoattractant agents, growth factors and cells also can be increased by treating tissues with glycosaminoglycan-degrading enzymes, both chondroitinases and heparinases. The enzymic removal of chondroitin sulfates from cell surfaces effectively increases the availability of growth factor receptors on the cell's surface. Selectively removing heparan sulfate from cell surfaces while leaving the extracellular matrix intact, conversely, inhibits cell proliferation by down-regulating the cell's response to growth factors. This is achieved by targeting **heparin**- or heparan sulfate-degrading activities to the cell surface. Targeting the **heparin**-degrading activity can be achieved by genetically engineering a ligand-binding functionality into the heparinase proteins, or by phys. controlling the localized enzyme concn. through the method of **administration**.

L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:11727 CAPLUS
DOCUMENT NUMBER: 118:11727
TITLE: Heparinase from Flavobacterium heparinum for **heparin** neutralization
INVENTOR(S): **Zimmermann, Joseph J.**; Lewis, N. Tracey; Heft, Robert A.
PATENT ASSIGNEE(S): Ibex Technologies, Inc., Can.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE
WO 9217203 A1 19921015 WO 1992-US2724 19920403
W: AU, CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE
US 5262325 A 19931116 US 1991-680330 19910404
AU 9217713 A1 19921102 AU 1992-17713 19920403
AU 658418 B2 19950413
EP 537325 A1 19930421 EP 1992-910865 19920403
EP 537325 B1 19991103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE
JP 05507297 T2 19931021 JP 1992-510024 19920403
JP 2542780 B2 19961009
CA 2083162 C 19980811 CA 1992-2083162 19920403
AT 186217 E 19991115 AT 1992-910865 19920403
ES 2141106 T3 20000316 ES 1992-910865 19920403
US 5338677 A 19940816 US 1993-153134 19931115

PRIORITY APPLN. INFO.: US 1991-680330 19910404
WO 1992-US2724 19920403

AB A heparinase derived from F. heparinum eliminates **heparin** interference of normal blood function. The heparinase is free of a component that inhibits coagulation. The heparinase is useful in vitro to eliminate the interference in hematol. assays due to the presence of **heparin** and for the in vivo neutralization of **heparin** during surgical procedures. It achieves neutralization faster and more completely than previous compns. and is stable for a long time. When rabbits were **administered** 250 IU **heparin**/kg, the activated clotting time (ACT) was increased from 180 to >999 s. When 2.5 IU heparinase/kg was injected over the next h, the ACT returned to normal. Heparinase was purified by affinity chromatog. and was eluted with a concd. eluent to elute a fraction free of the coagulation-inhibition component.

L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:13443 CAPLUS
DOCUMENT NUMBER: 110:13443
TITLE: Incompatibility of dacarbazine and **heparin** sodium
AUTHOR(S): Schroeder, Frank; **Zimmermann, Jutta**
CORPORATE SOURCE: Zentralapotheke, Zentralkrankenhaus., Bremen, 2800/1, Fed. Rep. Ger.
SOURCE: Pharm. Ztg. (1988), 133(36), 24, 26
CODEN: PHZIAP; ISSN: 0031-7136
DOCUMENT TYPE: Journal
LANGUAGE: German

AB The use of dacarbazine in oncol. studies leads to massive pain reactions and to decrease the pain **heparin** Na salt is usually **administered** i.v. The direct contact of both these drugs in an infusion system leads to the formation of turbidity of the solns. in catheters. As a temporary soln. to this problem, the **administration** of dacarbazine in the form of short infusion while avoiding the simultaneous **heparin administration** is recommended.

L4 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:292364 BIOSIS
DOCUMENT NUMBER: PREV200000292364
TITLE: Attenuation of wound healing processes.
AUTHOR(S): **Zimmermann, Joseph** (1); Vlodavsky, Israel; Bennett, Clark; **Danagher, Pamel**; Broughton, Richard
CORPORATE SOURCE: (1) Montreal Canada
ASSIGNEE: Ibex Technologies R and D, Inc., Montreal, Canada
PATENT INFORMATION: US 5997863 December 07, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 7, 1999) Vol. 1229, No. 1, pp. No pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

AB Glycosaminoglycans, including heparinases 1, 2 and 3 as well as chondroitinases AC and B from the Gram negative bacteria Flavobacterium heparinum, can be used either separately or in combination to manipulate cell proliferation. In one embodiment, heparinases are **administered** to degrade heparan sulfate components of the extracellular matrix, thereby allowing the **heparin** binding growth factors which are stored in the extracellular matrix to migrate to adjacent cells. The mobility of chemoattractant agents, growth factors and cells also can be increased by treating tissues with glycosaminoglycan degrading enzymes, both chondroitinases and heparinases. The enzymatic removal of chondroitin sulfates from cell surfaces effectively increases the availability of growth factor receptors on the cell's surface. Selectively removing heparan sulfate from cell surfaces while leaving the extracellular matrix intact, conversely, inhibits cell proliferation by down regulating the cell's response to growth factors. This is achieved by targeting **heparin** or heparan sulfate degrading activities to the cell surface. Targeting the **heparin** degrading activity can be achieved by genetically engineering a ligand binding functionality into the heparinase proteins, or by physically controlling the localized enzyme concentration through the method of **administration**.

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=> dis his

     (FILE 'HOME' ENTERED AT 09:28:02 ON 29 MAY 2002)

     FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 09:28:14 ON 29 MAY 2002
L1          3125 S BENNET D?/AU OR CAUCHON E?/AU OR FINK D?/AU OR GROUIX B?/AU O
L2            43 S L1 AND HEPARIN OR HEPARINSE
L3            21 DUP REM L2 (22 DUPLICATES REMOVED)
L4             7 S L3 (P) ADMINIST?
L5             0 S L4 (P) (IV OR INTRAVASCULAR?)

=> s l1 and (heparinase or heparin)
L6           59 L1 AND (HEPARINASE OR HEPARIN)

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7            29 DUP REM L6 (30 DUPLICATES REMOVED)

=> s l7 (P) administ?
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L32 (P) ADMINIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L34 (P) ADMINIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L36 (P) ADMINIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L38 (P) ADMINIST?'
L8             7 L7 (P) ADMINIST?

=> s l8 not l4
L9             0 L8 NOT L4

=> s (heparinase or heparinase?)
L10         3653 (HEPARINASE OR HEPARINASE?)

=> s l10 (10N) (administ?
UNMATCHED LEFT PARENTHESIS '10A) (ADMINIST?'
```

The number of right parentheses in a query must be equal to the number of left parentheses.

```
=> s l10 (10N) (administ?)
L11          41 L10 (10N) (ADMINIST?)

=> s l11 (P) (iv or intravascul?)
L12           0 L11 (P) (IV OR INTRAVASCUL?)

=> dup rem l11
PROCESSING COMPLETED FOR L11
L13          18 DUP REM L11 (23 DUPLICATES REMOVED)

=> s l13 not l4
L14          14 L13 NOT L4

=> dis l14 1-14 ibib abs kwic

L14  ANSWER 1 OF 14      MEDLINE
ACCESSION NUMBER:    2001682061      MEDLINE
DOCUMENT NUMBER:     21583162   PubMed ID: 11726421
TITLE:               A dose-determining trial of heparinase-I (Neutralase) for
                     heparin neutralization in coronary artery surgery.
AUTHOR:              Heres E K; Horrow J C; Gravlee G P; Tardiff B E; Luber J
                     Jr; Schneider J; Barragry T; Broughton R
CORPORATE SOURCE:    Allegheny General Hospital, Pittsburgh, Pennsylvania, USA.
SOURCE:              ANESTHESIA AND ANALGESIA, (2001 Dec) 93 (6) 1446-52, table
                     of contents.
                     Journal code: 1310650. ISSN: 0003-2999.
PUB. COUNTRY:        United States
                     (CLINICAL TRIAL)
                     Journal; Article; (JOURNAL ARTICLE)
                     (MULTICENTER STUDY)
LANGUAGE:            English
FILE SEGMENT:        Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:         200112
ENTRY DATE:          Entered STN: 20011203
                     Last Updated on STN: 20020123
                     Entered Medline: 20011213
AB   Heparinase-I, a specific heparin-degrading enzyme, may represent an
     alternative to protamine. We explored the dose of heparinase-I for
     efficacy and safety in patients undergoing coronary artery surgery. At the
     conclusion of cardiopulmonary bypass, subjects received 5, 7, or 10
     microg/kg of open-label heparinase-I instead of protamine. Activated
     clotting time (ACT) and its difference from a contemporaneous heparin-free
     sample (DeltaACT) at 3 min before and 3, 6, and 9 min after heparinase-I
     determined reversal efficacy. After surgery, we recorded hourly chest tube
     drainage. Systemic and pulmonary arterial blood pressure and cardiac
     output measurements before and immediately after heparinase-I were used to
     evaluate hemodynamic safety. Coagulation measurements included anti-factor
     Xa and anti-factor IIa activities. Forty-nine patients from seven
     institutions participated: 12 received 5 microg/kg, 21 received 7
     microg/kg, 4 received two doses of 7 microg/kg, 8 received 10 microg/kg,
     and 4 received two doses of 10 microg/kg. Treatment groups did not differ
     demographically. Median DeltaACT 9 min later was 11, 7, and 4 s for the 5,
     7, and 10 microg/kg groups, respectively. No adverse hemodynamic changes
     occurred with heparinase-I administration. The authors
     conclude that heparinase-I effectively restored the ACT after
     cardiopulmonary bypass. This effect appeared to be dose dependent.
     IMPLICATIONS: Heparinase-I (Neutralase(TM)) successfully restored
     activated coagulation time with no adverse hemodynamic events in patients
     undergoing coronary artery surgery with cardiopulmonary bypass in an
     open-label dose-determining trial.
AB   . . . 11, 7, and 4 s for the 5, 7, and 10 microg/kg groups,
     respectively. No adverse hemodynamic changes occurred with
     heparinase-I administration. The authors conclude that
     heparinase-I effectively restored the ACT after cardiopulmonary
     bypass. This effect appeared to be dose dependent. IMPLICATIONS:
     Heparinase-I (Neutralase(TM)) successfully restored activated. . .

L14  ANSWER 2 OF 14      MEDLINE
ACCESSION NUMBER:    2001321665      MEDLINE
DOCUMENT NUMBER:     21201502   PubMed ID: 11304642
TITLE:               Analysis of the hemodynamic effects of heparinase I and
                     protamine sulfate in the systemic and hindlimb vascular
                     beds of the male rat.
AUTHOR:              Jahr J S; Stuart J S
CORPORATE SOURCE:    Department of Anesthesiology, University of California
                     Davis Medical Center, Sacramento, CA 95817, USA.
SOURCE:              AMERICAN JOURNAL OF THERAPEUTICS, (2000 Nov) 7 (6) 353-7.
                     Journal code: DB7; 9441347. ISSN: 1075-2765.
PUB. COUNTRY:        United States
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200106
ENTRY DATE:          Entered STN: 20010611
                     Last Updated on STN: 20010611
                     Entered Medline: 20010607
AB   The effects of heparinase I and protamine sulfate on the mean arterial
     pressure and hindlimb perfusion pressure in the male rat were studied.
     With institutional approval, 21 male Sprague-Dawley rats were
     anesthetized, and the carotid artery and abdominal aorta were cannulated
     by cutdown. To isolate the hindlimb, a semi-closed peristaltic perfusion
     circuit was used. Heparinase I or protamine sulfate was injected into the
     hindlimb vascular bed, and changes in mean arterial pressure and hindlimb
     perfusion pressure were recorded. Analysis of variance with a post hoc
     Scheffe's test was used for statistical analysis, and a P value less
     than.05 was considered significant. Increasing doses of heparinase I
     caused a small but significant decrease in mean arterial pressure only at
     the two highest doses. At all doses, hindlimb perfusion pressure was
     significantly less than the baseline value and than the value with saline
     administration at 1 minute. At the clinically applicable doses of
     heparinase I (0.625 and 1.25 IU/kg), the decrease in hindlimb
     perfusion pressure was less than 7. At the next two higher doses, the
     change was less than 15%. The vehicle of heparinase caused a significant
     decrease in mean arterial pressure (from -15% to -30%) and hindlimb
     perfusion pressure (from -10% to -20%). Increasing doses of protamine
     sulfate caused an increase in hindlimb perfusion pressure from baseline,
     including a 58% change with the 10-mg/kg dose. There was a transient
     decrease in mean arterial pressure, which peaked 4 to 5 minutes after
     injection, to a 21% decrease from baseline with the 5- and 10-mg/kg doses.
```

Heparinase I caused vasodilation in the hindlimb and decreased mean arterial pressure only at supraclinical doses. Protamine sulfate caused a significant dose-dependent increase in hindlimb vascular resistance and a transitory decrease in mean arterial pressure.

AB . . . . doses. At all doses, hindlimb perfusion pressure was significantly less than the baseline value and than the value with saline **administration** at 1 minute. At the clinically applicable doses of **heparinase** I (0.625 and 1.25 IU/kg), the decrease in hindlimb perfusion pressure was less than 7. At the next two higher. . .

L14 ANSWER 3 OF 14 MEDLINE
ACCESSION NUMBER: 2001141460 MEDLINE
DOCUMENT NUMBER: 21091197 PubMed ID: 11159222
TITLE: Pentalyte does not decrease heparinoid release but does decrease circulating thrombotic mediator activity associated with aortic occlusion-reperfusion in rabbits.
AUTHOR: Nielsen V G; Armstead V E; Geary B T; Opentanova I L
CORPORATE SOURCE: Department of Anesthesiology, Division of Cardiothoracic Anesthesia, The University of Alabama at Birmingham, Birmingham, Alabama 35249, USA.. vance.nielsen@ccc.uab.edu
CONTRACT NUMBER: KO8-GM00686 (NIGMS)
SOURCE: ANESTHESIA AND ANALGESIA, (2001 Feb) 92 (2) 314-9. Journal code: 4R8; 1310650. ISSN: 0003-2999.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308

AB Hemorrhage and thrombosis are associated with major vascular and trauma surgery. Release of heparinoids and thrombotic mediators may contribute to these complications and have been described in rabbits after aortic occlusion-reperfusion. We hypothesized that the resuscitative fluid used could reduce heparinoid and thrombotic mediator release after aortic occlusion-reperfusion in rabbits as assessed by thromboelastographic variables (R, reaction time; alpha, angle; and G, a measure of clot strength). Anesthetized rabbits were administered lactated Ringer's solution (n = 8) or PentaLyte (n = 8) at reperfusion after 30 min of ischemia. Blood was obtained before ischemia and after 30 min of reperfusion for thromboelastography under four conditions: 1) unmodified sample, 2) platelet inhibition, 3) heparinase, and 4) platelet inhibition and heparinase. During reperfusion, unmodified samples demonstrated a significant increase in R and decrease in alpha and G that was not affected by PentaLyte. In the presence of heparinase, no significant fluid-specific thromboelastographic differences were noted. However, thrombotic mediator release (discerned by a decrease in R and an increase in alpha) during reperfusion in samples with platelet inhibition and **heparinase** was significantly attenuated by PentaLyte. PentaLyte **administration** does not decrease heparinoid release but does decrease thrombotic mediator release after aortic occlusion-reperfusion.

AB . . . release (discerned by a decrease in R and an increase in alpha) during reperfusion in samples with platelet inhibition and **heparinase** was significantly attenuated by PentaLyte. PentaLyte **administration** does not decrease heparinoid release but does decrease thrombotic mediator release after aortic occlusion-reperfusion.

L14 ANSWER 4 OF 14 MEDLINE
ACCESSION NUMBER: 2001034941 MEDLINE
DOCUMENT NUMBER: 20534203 PubMed ID: 11083232
TITLE: Influence of the endothelial glycocalyx on cerebral blood flow in mice.
AUTHOR: Vogel J; Sperandio M; Pries A R; Linderkamp O; Gaehtgens P; Kuschinsky W
CORPORATE SOURCE: Department of Physiology and Pathophysiology, University of Heidelberg, Germany.
SOURCE: JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, (2000 Nov) 20 (11) 1571-8. Journal code: HNL. ISSN: 0271-678X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001130

AB The endothelial surface layer (glycocalyx) of cerebral capillaries may increase resistance to blood flow. This hypothesis was investigated in mice by intravenous **administration** of **heparinase** (2500 IU/kg body weight in saline), which cleaves proteoglycan junctions of the glycocalyx. Morphology was investigated by transmission electron microscopy. Cerebral perfusion velocity was recorded before and during heparinase or saline treatment using laser-Doppler flowmetry. In addition, cerebral blood flow (CBF) was measured 10 minutes after heparinase or saline treatment using the iodo[14C]antipyrine method. Laser-Doppler flowmetry and CBF measurements were performed during normocapnia and severe hypercapnia (PCO2: 120 mm Hg). After heparinase, morphology showed a reduced thickness of the glycocalyx in cortical microvessels by 43% ($P < 0.05$) compared with saline-treated controls. Under normocapnic conditions, a 15% ($P < 0.05$) transient increase of cerebral flow velocity occurred 2.5 to 5 minutes after heparinase injection. Laser-Doppler flow and CBF returned to control values ten minutes after the injection. However, during severe hypercapnia, heparinase treatment resulted in a persisting increase in laser-Doppler flow (6%, $P < 0.05$) and CBF (30%, $P < 0.05$). These observations indicate the existence of a flow resistance in cerebral capillaries exerted by the glycocalyx. The transient nature of the CBF increase during normocapnia may be explained by a vascular compensation that is exhausted during severe hypercapnia.

AB . . . surface layer (glycocalyx) of cerebral capillaries may increase resistance to blood flow. This hypothesis was investigated in mice by intravenous **administration** of **heparinase** (2500 IU/kg body weight in saline), which cleaves proteoglycan junctions of the glycocalyx. Morphology was investigated by transmission electron microscopy.. . .

L14 ANSWER 5 OF 14 MEDLINE
ACCESSION NUMBER: 2000286215 MEDLINE
DOCUMENT NUMBER: 20286215 PubMed ID: 10825314
TITLE: Rapid evaluation of coagulopathies after cardiopulmonary bypass in children using modified thromboelastography.

AUTHOR: Miller B E; Guzzetta N A; Tosone S R; Levy J H
CORPORATE SOURCE: Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
SOURCE: ANESTHESIA AND ANALGESIA, (2000 Jun) 90 (6) 1324-30.
Journal code: 4R8; 1310650. ISSN: 0003-2999.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000616

AB Complex coagulopathies follow cardiopulmonary bypass (CPB) in children. However, objective laboratory data that can be acquired rapidly to guide their management are lacking. Because thromboelastography has proven useful in this regard, we evaluated the use of celite or tissue factor (TF) activation and heparinase modification of blood samples to allow rapid determination of thromboelastogram data in children younger than 2 yr undergoing CPB. Celite or TF activation shortened the initiation of clotting and, thus, the time required for the important thromboelastogram alpha and maximum amplitude values to begin evolving. Although thromboelastogram alpha and maximum amplitude values were increased with these activators, correlations persisted between platelet count or fibrinogen level and each of these values. The additional use of heparinase allowed thromboelastograms to be obtained during CPB with values not different from those obtained without **heparinase** after protamine **administration**. Therefore, celite- or TF-activated, **heparinase**-modified thromboelastograms begun during CPB allow objective data to be available by the conclusion of protamine administration to help restore hemostasis after CPB in children. Thromboelastography identified transient fibrinolysis during CPB in some children that resolved by the conclusion of protamine administration. Future investigations of the effectiveness of modified thromboelastography-guided coagulopathy management after CPB in children are needed. Implications: Thromboelastography is useful in assessing the coagulopathies that follow cardiopulmonary bypass in children. Modifying blood samples with celite or tissue factor and heparinase allows thromboelastography begun before the termination of cardiopulmonary bypass to become a rapid point-of-care monitor to provide objective data for guiding blood component therapy to manage these coagulopathies.

AB . . . The additional use of heparinase allowed thromboelastograms to be obtained during CPB with values not different from those obtained without **heparinase** after protamine **administration**. Therefore, celite- or TF-activated, **heparinase**-modified thromboelastograms begun during CPB allow objective data to be available by the conclusion of protamine administration to help restore hemostasis. . .

L14 ANSWER 6 OF 14 MEDLINE
ACCESSION NUMBER: 1999384172 MEDLINE
DOCUMENT NUMBER: 99384172 PubMed ID: 10454476
TITLE: Ex vivo reversal of heparin-mediated cardioprotection by heparinase after ischemia and reperfusion.
AUTHOR: Kilgore K S; Tanhehco E J; Naylor K B; Lucchesi B R
CORPORATE SOURCE: Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan, USA.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1999 Sep) 290 (3) 1041-7.
Journal code: JP3; 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990921

AB Glycosaminoglycans, including heparin, have been demonstrated both in vitro and in vivo to protect the ischemic myocardium against reperfusion injury. In the present study, we sought to determine whether the cardioprotective effects of heparin **administration** could be reversed by the heparin-degrading enzyme **heparinase**. New Zealand white rabbits were pretreated with heparin (300 U/kg i.v.) or vehicle (saline). Two hours after treatment, hearts were removed, perfused on a Langendorff apparatus, and subjected to 25 min of global ischemia, followed by 45 min of reperfusion. Hemodynamic variables were obtained before ischemia (baseline) and every 10 min throughout the reperfusion period. Compared with vehicle-treated rabbits, the left ventricular end-diastolic and left ventricular developed pressures were improved significantly ($p < .05$) in the heparin-treated group. Ex vivo **administration** of **heparinase** (5 U/ml) immediately before the onset of global ischemia was associated with a reversal of the heparin-mediated cardioprotection. The uptake of a radiolabeled antibody to the intracellular protein myosin and creatine kinase release were used to determine membrane integrity and discriminate between viable and nonviable myocardial tissue. The uptake of radiolabeled antimyosin antibody and release of creatine kinase after reperfusion were increased in heparin-pretreated hearts exposed to heparinase, indicating a loss of membrane integrity and increased myocyte injury. These results demonstrate that neutralization of heparin by heparinase promotes increased myocardial injury after reperfusion of the ischemic myocardium.

AB . . . . the ischemic myocardium against reperfusion injury. In the present study, we sought to determine whether the cardioprotective effects of heparin **administration** could be reversed by the heparin-degrading enzyme **heparinase**. New Zealand white rabbits were pretreated with heparin (300 U/kg i.v.) or vehicle (saline). Two hours after treatment, hearts were. . . the left ventricular end-diastolic and left ventricular developed pressures were improved significantly ($p < .05$) in the heparin-treated group. Ex vivo **administration** of **heparinase** (5 U/ml) immediately before the onset of global ischemia was associated with a reversal of the heparin-mediated cardioprotection. The uptake. . .

L14 ANSWER 7 OF 14 MEDLINE
ACCESSION NUMBER: 1998300542 MEDLINE
DOCUMENT NUMBER: 98300542 PubMed ID: 9636913
TITLE: Thromboelastography with heparinase in orthotopic liver transplantation.
AUTHOR: Pivalizza E G; Abramson D C; King F S Jr
CORPORATE SOURCE: Department of Anesthesiology, University of Texas Health Science Center, Houston 77030, USA.

SOURCE: JOURNAL OF CARDIOTHORACIC AND VASCULAR ANESTHESIA, (1998 Jun) 12 (3) 305-8.
Journal code: A6I; 9110208. ISSN: 1053-0770.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980909

AB OBJECTIVE: To investigate the role of heparin in the postreperfusion coagulopathy during liver transplantation with heparinase-guided thromboelastography. DESIGN: A prospective, interventional study. SETTING: A university-affiliated hospital. PARTICIPANTS: Twenty-six patients undergoing orthotopic liver transplantation (OLT). INTERVENTIONS: Blood drawn at five intervals for thromboelastography assessment with native (12 patients) or celite blood (14 patients) compared with simultaneous thromboelastography traces with added heparinase. MAIN RESULTS: In the native samples, the prolonged R (reaction) and K (coagulation) time and decreased alpha angle were corrected in heparinase thromboelastograph traces immediately before reperfusion and 10 minutes postreperfusion. In the celite-accelerated samples, the heparinase traces showed correction of the R and K times and alpha angle only at the 10-minute postreperfusion stage. In seven patients who had thromboelastography performed after protamine **administration**, there were no differences between celite and **heparinase**-celite traces. CONCLUSIONS: Heparinase-treated thromboelastography offered compelling evidence for the presence of heparin-like activity after liver graft reperfusion. The objective evidence provided by this modification of thromboelastography-guided protamine administration and was useful in identifying one of the many potential causes of postreperfusion bleeding in patients undergoing OLT.

AB . . . K times and alpha angle only at the 10-minute postreperfusion stage. In seven patients who had thromboelastography performed after protamine **administration**, there were no differences between celite and **heparinase**-celite traces. CONCLUSIONS: Heparinase-treated thromboelastography offered compelling evidence for the presence of heparin-like activity after liver graft reperfusion. The objective evidence. . .

L14 ANSWER 8 OF 14 MEDLINE
ACCESSION NUMBER: 97097806 MEDLINE
DOCUMENT NUMBER: 97097806 PubMed ID: 8942349
TITLE: Heparinase-guided thrombelastography in an anticoagulated parturient.
AUTHOR: Abramson D C; Abouleish E I; Pivalizza E G; Luehr S L; Myers T; Phillips M D
CORPORATE SOURCE: Department of Anesthesiology, University of Texas Medical School at Houston 77030, USA.
SOURCE: BRITISH JOURNAL OF ANAESTHESIA, (1996 Oct) 77 (4) 556-8.
Journal code: AUO; 0372541. ISSN: 0007-0912.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19980206
Entered Medline: 19961230

AB We describe the use of heparinase-guided thrombelastography in the assessment of a parturient who had been anticoagulated with heparin for suspected thromboembolic disease. Reversal of the heparin effect in the **heparinase**-treated sample facilitated **administration** of protamine and successful subarachnoid analgesia for delivery.

AB . . . of a parturient who had been anticoagulated with heparin for suspected thromboembolic disease. Reversal of the heparin effect in the **heparinase**-treated sample facilitated **administration** of protamine and successful subarachnoid analgesia for delivery.

L14 ANSWER 9 OF 14 MEDLINE
ACCESSION NUMBER: 96239965 MEDLINE
DOCUMENT NUMBER: 96239965 PubMed ID: 8815578
TITLE: Low molecular weight heparin is responsible for the anti-Xa activity of Desmin 370.
AUTHOR: Brieger D; Dawes J
CORPORATE SOURCE: Applied Research Group, The Heart Research Institute, Sydney, Australia.
SOURCE: THROMBOSIS AND HAEMOSTASIS, (1996 Feb) 75 (2) 286-91.
Journal code: VQ7; 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961022
Last Updated on STN: 19980206
Entered Medline: 19961010

AB Dermatan sulphate does not catalyse the inactivation of factor Xa. However, the low molecular weight (LMW) dermatan sulphate Desmin 370 has been shown to generate circulating anti-Xa activity following administration to humans. Using a single batch of Desmin 370, we measured 3 U/mg of anti-Xa activity by amidolytic assay in vitro. The material responsible for this activity had a lower molecular weight range (6000 and 1800 Da) than Desmin 370 and was more highly sulphated than the bulk of the drug. Heparinase digestion of Desmin 370 eliminated 90% of the in vitro anti-Xa activity without significantly interfering with its ability to potentiate inactivation of thrombin by HCII, suggesting that the anti-Xa activity is not due to dermatan sulphate and is probably heparin. When 125I-labelled Desmin 370 together with 40 mg/kg carrier drug was administered intravenously to a rabbit, anti-Xa activity was readily detectable in the plasma for up to 10 h and had a longer half-life than the sulphated radiolabel. Most of this anticoagulant activity was recovered from the plasma by Polybrene affinity chromatography and was probably a sulphated glycosaminoglycan. **Administration** of the **heparinase**-digested drug to a rabbit resulted in 70% less anti-Xa activity than the undigested drug. We conclude that Desmin 370 contains detectable quantities of biologically active low molecular weight heparin, which is responsible for persistent anti-Xa activity following intravenous administration.

AB . . . Most of this anticoagulant activity was recovered from the plasma by Polybrene affinity chromatography and was probably a sulphated

glycosaminoglycan. **Administration** of the **heparinase** -digested drug to a rabbit resulted in 70% less anti-Xa activity than the undigested drug. We conclude that Desmin 370 contains. . .

L14 ANSWER 10 OF 14 MEDLINE
ACCESSION NUMBER: 87100328 MEDLINE
DOCUMENT NUMBER: 87100328 PubMed ID: 3801083
TITLE: Effect of very low molecular weight heparin-derived oligosaccharides on lipoprotein lipase release in rabbits.
AUTHOR: Merchant Z M; Erbe E E; Eddy W P; Patel D; Linhardt R J
SOURCE: ATHEROSCLEROSIS, (1986 Nov) 62 (2) 151-8.
Journal code: 95X; 0242543. ISSN: 0021-9150.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198701
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19980206
Entered Medline: 19870130

AB Oligosaccharide fragments of heparin were prepared using flavobacterial **heparinase**. Following sizing, these oligosaccharide fractions were **administered** (i.v.) to rabbits and were examined for their ability to release lipoprotein lipase. The decasaccharides (dp = 10, Mr avg = 2,800) were the smallest oligosaccharides which resulted in substantial lipase release. The plasma lipase levels obtained with decasaccharides were comparable to low molecular weight heparin and one-third those obtained when heparin was administered at an equivalent dose. The peak plasma lipase concentration was observed 10 min following heparinization and fell off rapidly over the 60-min time course. The lipase release activity paralleled the in vivo pharmacokinetics of the heparin and decasaccharide sample as determined by monitoring their anti-Factor Xa activity. No activation of purified bovine milk lipoprotein lipase or plasma lipase was detectable at the concentrations studied, indicating that the increase in circulating lipolytic activity was due entirely to release. Lipoprotein lipase accounted for a major portion of the released activity with hepatic triglyceride lipase representing the remainder of the lipolytic activity. The sized decasaccharide sample was characterized with regards to its structure and anticoagulant activity. The decasaccharides exhibited reduced anticoagulant activity possibly making it a better drug candidate in the treatment of atherosclerosis.
AB Oligosaccharide fragments of heparin were prepared using flavobacterial **heparinase**. Following sizing, these oligosaccharide fractions were **administered** (i.v.) to rabbits and were examined for their ability to release lipoprotein lipase. The decasaccharides (dp = 10, Mr avg. . .

L14 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:676971 CAPLUS
DOCUMENT NUMBER: 135:221282
TITLE: Use of heparinase III in cancer treatment and inhibition of tumor cell growth
INVENTOR(S): Dongfang, Liu; Pojasek, Kevin; Shriver, Zachary; Holley, Kristine; El-Shabrawi, Yosuf; Venkataraman, Ganesh; Sasisekharan, Ram
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001066772	A2	20010913	WO 2001-US7464	20010308

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
PRIORITY APPLN. INFO.: US 2000-187846P P 20000308

AB The invention relates to heparinase III and mutants thereof. Modified forms of heparinase III having reduced enzymic activity which are useful for a variety of purposes, including sequencing of heparin-like glycosaminoglycans (HLGAGs), removing active heparan sulfate from a soln., inhibition of angiogenesis, etc. have been discovered according to the invention. The invention in other aspects relates to methods of treating cancer and inhibiting tumor cell growth and/or metastasis using heparinase III, or products produced by enzymic cleavage by heparinase III of HLGAGs.
IT Antitumor agents
(**heparinase** II **administration** with; use of **heparinase** III in cancer treatment and inhibition of tumor cell growth)

L14 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1983:27563 CAPLUS
DOCUMENT NUMBER: 98:27563
TITLE: In vivo activity of microbial heparinase
AUTHOR(S): Langer, R.; Linhardt, R. J.; Larsen, A. K.; Cooney, C. L.; Tapper, D.; Klein, M.
CORPORATE SOURCE: Dep. Nutr. Food Sci., MIT, Cambridge, MA, USA
SOURCE: Trans. - Am. Soc. Artif. Intern. Organs (1982), 28, 387-90
CODEN: TAIOAL; ISSN: 0066-0078
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In rabbits, i.v. **administration** of **heparinase** [9025-39-2] (0.5 mg) either 1 min before or 1 min after heparin [9005-49-6] administration substantially decreased the activated partial thromboplastin time (aPTT). Blood from heparinized dogs was passed through a filter of immobilized heparinase. Within 2 min or 1 pass through the filter nearly all the anticoagulant activity of heparin (aPTT) was destroyed. Antibodies to heparin were not detected in the blood of the dogs 2 mo after the expt.
AB In rabbits, i.v. **administration** of **heparinase** [9025-39-2] (0.5 mg) either 1 min before or 1 min after heparin [9005-49-6] administration substantially decreased the activated partial thromboplastin time (aPTT). Blood from heparinized dogs was passed through a filter of immobilized heparinase. Within 2 min or 1 pass through the filter nearly all the anticoagulant activity of heparin (aPTT) was destroyed. Antibodies to heparin were not detected in the blood of the dogs 2 mo after the expt.

L14 ANSWER 13 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97017864 EMBASE
DOCUMENT NUMBER: 1997017864
TITLE: Do heparinase thrombelastographs predict postoperative bleeding?.
AUTHOR: Mashburn P.; Ecklund J.; Riley J.
CORPORATE SOURCE: J. Ecklund, MUSC-ECT, 101 Doughty St., Charleston, SC 29401, United States
SOURCE: Journal of Extra-Corporeal Technology, (1996) 28/4 (185-190).
Refs: 10
ISSN: 0022-1058 CODEN: JEXCBD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Postoperative hemorrhage is a major cause of morbidity and mortality in patients who undergo cardiopulmonary bypass (CPB). The thrombelastograph (TEG) is a viscoelastic whole blood test that measures clot dynamics from clot formation through clot lysis. Previous studies have shown that post-bypass TEGs are accurate predictors of postoperative bleeding. TEGs from heparinized blood reversed with heparinase may be employed during CPB to evaluate coagulation. CPB heparinase TEGs may allow for earlier recognition of patients who may bleed after bypass. Earlier TEG analysis would allow targeting of specific therapies to begin before the patient bleeds excessively. Fifty-four **heparinase** TEGs during warming and fifty-four native TEGs post-protamine **administration** were collected. Parameters evaluated were R, K, alpha angle, MA, MA60, coagulation index, activated clotting time, hematocrit, prothrombin time, partial thromboplastin time, thrombin time, fibrinogen concentration, platelet count, blood loss during and after CPB, and blood and blood product **administration**. Coagulation indexes for CPB **heparinase** TEGs that were less than -2 or heparinase TEGs that were fibrinolytic were 87% accurate in predicting patients with excessive intraoperative blood loss, but were not predictive of blood product administration. The sensitivity was 12.5% and the specificity was 100% in predicting excessive intraoperative bleeding. Post-protamine coagulation index inversely correlated with intraoperative red blood cell administration ($r=0.403$, $p<0.05$), but was not predictive. Patients with fibrinolytic TEGs required blood products to compensate for expected blood loss associated with the fibrinolytic state. Simultaneous routine coagulation tests did not correlate significantly with blood loss or blood product administration, nor were they predictive. The findings of this study suggest that the presence of fibrinolysis in either a heparinase TEG on bypass or a post-protamine TEG is the most important predictor of blood and blood product administration. But, since only 20% of the patients in the study exhibited fibrinolytic TEGs, a study that included a much larger sample of patients would need to be done to confirm this finding.
AB . . . bleed after bypass. Earlier TEG analysis would allow targeting of specific therapies to begin before the patient bleeds excessively. Fifty-four **heparinase** TEGs during warming and fifty-four native TEGs post-protamine **administration** were collected. Parameters evaluated were R, K, alpha angle, MA, MA60, coagulation index, activated clotting time, hematocrit, prothrombin time, partial thromboplastin time, thrombin time, fibrinogen concentration, platelet count, blood loss during and after CPB, and blood and blood product **administration**. Coagulation indexes for CPB **heparinase** TEGs that were less than -2 or heparinase TEGs that were fibrinolytic were 87% accurate in predicting patients with excessive. . .

L14 ANSWER 14 OF 14 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:151746 BIOSIS
DOCUMENT NUMBER: PREV200200151746
TITLE: Neutralization of the anticoagulant and hemorrhagic effects of an ultra-low molecular weight heparin (OP2000) by heparinase-I: Potential clinical implications.
AUTHOR(S): Shadid, H. (1); Daud, A. N.; Iqbal, O.; Ahmad, S.; Hoppensteadt, D. A.; Demir, M.; Walenga, J. M.; Ward, D. P.; Fareed, J. (1)
CORPORATE SOURCE: (1) Pharmacology, Loyola University of Chicago, Maywood, IL USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 2, pp. 99b. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB An ultra-low molecular weight heparin, OP2000, from porcine mucosal heparin has shown better efficacy than unfractionated heparin (UFH) in the management of unstable angina (Clin. Cardiol. 22:213-7, 1999). This drug is currently being developed for the treatment of inflammatory bowel disease, particularly in ulcerative colitis. The treatment dosage for both of these indications is 150 mg/day. While the relative bleeding effects of this agent are lower than UFH because of the significant anti-IIa component and release of tissue factor pathway inhibitor (TFPI), the hemorrhagic potential exists. Protamine sulfate produces a partial neutralization of this agent. In this study, heparinase-I was used to neutralize the anticoagulant and bleeding effect of this agent in experimental and animal models. OP2000 was supplemented to whole blood in a concentration range of 0-100 mcg/ml. Activated clotting time (ACT) and thromboelastography (TEG) tests were performed to study the anticoagulant effects of OP2000. A concentration-dependent increase in the ACT and modification of the TEG parameters were noted. The neutralizing effect of heparinase-I was studied in the concentration range of 0.05-5.0 U/ml. It was observed that heparinase-I at concentration of 2 U/ml produced a complete neutralization of the anticoagulant effect of OP2000. Similarly, in the plasma-based preparations, neutralization of the anticoagulant effect of OP2000 was noted in the activated partial thromboplastin time (aPTT), Heptest, and anti-IIa activities. The molecular profiling of OP2000 by GPC-HPLC prior to and after the heparinase digestion revealed marked differences. The average molecular weight was reduced to di- and tri-saccharide components. At a dosage of 10 mg/kg i.v., OP2000 produced prolongation of the bleeding time in animal models (rats, rabbits, primates). **Administration** of **heparinase**-I at 0.25 U/kg markedly reversed the bleeding effects of these animal models. In contrast to the heparinase-I studies, protamine sulfate exhibited partial neutralization of OP2000 in these models. These results suggest that OP2000 and related oligosaccharides can be effectively neutralized by hepaarinase-I. Thus, if this agent is used at high dosages in percutaneous interventions or other surgical procedures, heparinase-I may be an

effective antagonist for the neutralization of this compound.
AB. . . At a dosage of 10 mg/kg i.v., OP2000 produced prolongation of the bleeding time in animal models (rats, rabbits, primates). **Administration** of **heparinase**-I at 0.25 U/kg markedly reversed the bleeding effects of these animal models. In contrast to the heparinase-I studies, protamine sulfate. . .

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(FILE 'HOME' ENTERED AT 09:28:02 ON 29 MAY 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 09:28:14 ON 29 MAY 2002
L1 3125 S BENNET D?/AU OR CAUCHON E?/AU OR PINK D?/AU OR GROUIX B?/AU O
L2 43 S L1 AND HEPARIN OR HEPARINSE
L3 21 DUP REM L2 (22 DUPLICATES REMOVED)
L4 7 S L3 (P) ADMINIST?
L5 0 S L4 (P) (IV OR INTRAVASCULAR?)
L6 59 S L1 AND (HEPARINASE OR HEPARIN)
L7 29 DUP REM L6 (30 DUPLICATES REMOVED)
L8 7 S L7 (P) ADMINIST?
L9 0 S L8 NOT L4
L10 3653 S (HEPARINASE OR HEPARINASE?)
L11 41 S L10 (10N) (ADMINIST?)
L12 0 S L11 (P) (IV OR INTRAVASCUL?)
L13 18 DUP REM L11 (23 DUPLICATES REMOVED)
L14 14 S L13 NOT L4

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LE 'HOME' ENTERED AT 09:28:02 ON 29 MAY 2002)

     FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 09:28:14 ON 29 MAY 2002
L1          3125 S BENNET D?/AU OR CAUCHON E?/AU OR FINK D?/AU OR GROUIX B?/AU O
L2            43 S L1 AND HEPARIN OR HEPARINSE
L3            21 DUP REM L2 (22 DUPLICATES REMOVED)
L4             7 S L3 (P) ADMINIST?
L5             0 S L4 (P) (IV OR INTRAVASCULAR?)
L6            59 S L1 AND (HEPARINASE OR HEPARIN)
L7            29 DUP REM L6 (30 DUPLICATES REMOVED)
L8             7 S L7 (P) ADMINIST?
L9             0 S L8 NOT L4
L10         3653 S (HEPARINASE OR HEPARINASE?)
L11           41 S L10 (10N) (ADMINIST?)
L12            0 S L11 (P) (IV OR INTRAVASCUL?)
L13           18 DUP REM L11 (23 DUPLICATES REMOVED)
L14           14 S L13 NOT L4

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